



## DECLARATION OF KATHERINE R. SPINDLER, PH.D.

I, Katherine R. Spindler, the undersigned, do hereby declare as follows:

1. I am a Professor in the Department of Microbiology and Immunology at the University of Michigan Medical School. My *curriculum vitae* details my professional experience and education. (Ex. 2011).
2. Prior to coming to the University of Michigan in 2002, I held various positions in the Department of Genetics of the University of Georgia. I started as an Assistant Professor there in 1985, was promoted to Associate Professor in 1992, and was promoted to full Professor in 1998. I received a bachelor's degree in Microbiology from Purdue University in 1975, and a doctorate degree in Biology from the University of California, San Diego in 1981.
3. Since receiving my Ph.D., I have focused my research on adenoviruses, and in particular mouse adenovirus type 1. I have served as a reviewer of manuscripts for several journals in the field of virology since 1985 and as a member of the editorial board of the journal *Virology* since 2001 and *Journal of Virology* since 2006. I have authored numerous publications and abstracts in the field of adenoviruses. A list of my publications is set forth in my *curriculum vitae*. (Ex. 2011).
4. I have been asked by Morrison & Foerster LLP to prepare this report in connection with the pending interference proceedings relating to United States Patent No. 6,492,343 B1, "Porcine Adenovirus Type 3 Genome," issued to Reddy et al. on Dec. 10, 2002 ("the '343 patent") and United States Application Serial No. 09/485,512 ("the '512 application") by Johnson et al.

5. In preparing this report, I have considered the following documents and patents:

- The '343 patent (Ex. 2001);

Reddy EXHIBIT 2009  
Reddy v. Johnson  
Interference 105,358

- The '512 application (Ex. 2002);
- Australian Provisional Patent Application No. PO 8560 filed August 14, 1997 by Johnson et al. (Ex. 2003);
- Unamended PCT Patent Application No. PCT/AU98/00648 filed August 14, 1998 by Johnson et al. (Ex. 2004);
- List of pending claims in the '512 patent application (Declaration of Interference, Ex. 2005);
- Prosecution history of the '512 patent application (including Exs. 2031-2033);
- Amended PCT Patent Application No. PCT/AU98/00648 filed November 11, 1999 (Ex. 2034); and
- Other publications listed in this declaration (Ex. 2014-2030, 2035-2036).

6. I have been informed by Morrison & Foerster LLP of the following facts regarding the present interference proceedings:

- Count 1 in the interference corresponds to claim 21 of the Reddy '343 patent (Ex. 2001) or claim 30 of the Johnson '512 application (Ex. 2002).
- Claim 21 of the '343 patent recites:  
21. The recombinant PAV3 vector according to claim 13 wherein the heterologous nucleotide sequence is inserted in the E3 region.
- Claim 21 depends from independent claim 13<sup>1</sup>. Combining the limitations of claims 21 and 13, claim 21 corresponds to:  
a recombinant PAV3 vector comprising a PAV3 genome capable of duplex formation under conditions of high stringency to the

<sup>1</sup> Claim 13 of the '343 patent (Ex. 2001) recites: A recombinant PAV3 vector comprising a PAV3 genome capable of duplex formation under conditions of high stringency to the PAV3 genome as depicted in SEQ ID NO:1, or a complement thereof and at least one heterologous nucleotide sequence, wherein the heterologous nucleotide sequence is inserted in a region selected from the group consisting of the E1 region, the E3 region, the E4 region and the region between E4 and the right end of the genome.

PAV3 genome as depicted in SEQ ID NO:1, or a complement thereof and at least one heterologous nucleotide sequence, wherein the heterologous nucleotide sequence is inserted in the E3 region.

- In the alternative, Count 1 also corresponds to claim 30 of the '512 application

(Ex. 2002) which recites:

30. A recombinant vector as claimed in claim 2 wherein said heterologous DNA is stably integrated into the adenovirus E3 region of the genome at map units from about 81 to about 84.

- Claim 30 of the '512 application (Ex. 2002) depends from claim 2<sup>2</sup>. Combining the limitations of claims 30 and 2, claim 30 of the '512 application corresponds to:

a recombinant vector including a recombinant porcine adenovirus stably incorporating, and expressing heterologous DNA wherein said heterologous DNA is incorporated into a site consisting of the adenovirus E3 region of the genome at map units from about 81 to about 84 .

- Count 2 of the interference corresponds to claim 28 of the '512 application (Ex. 2002) which recites:

28. A recombinant vector as claimed in claim 2 wherein said heterologous DNA is stably integrated into the right hand end of the genome at map units from about 97 to about 99.5.

- Claim 28 also depends from claim 2 of the '512 application (Ex. 2002) and combining the limitations of claims 2 and 28, claim 28 (Count 2) corresponds to:

a recombinant vector including a recombinant porcine adenovirus stably incorporating, and expressing heterologous DNA wherein said heterologous DNA is stably integrated into the right hand end of the genome at map units from about 97 to about 99.5 of PAV3.

7. Further, I have been informed that:

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<sup>2</sup> Claim 2 of the '512 application (Ex. 2002) recites: A recombinant vector including a recombinant porcine adenovirus stably incorporating, and expressing heterologous DNA wherein said heterologous DNA is incorporated into a site selected from the group consisting of one or more mapping units selected from the group consisting of mapping units 50-55, 55-65, 72-85, 81-84, and 97-99.5 of PAV3.

- My analysis should be conducted from the perspective of the state of the art in the time period 1996 to 1999; and
- To determine whether a patent application meets the standards required to support certain claims, I must consider (1) the level of ordinary skill in the pertinent art, (2) the scope and content of the disclosure, and (3) whether the disclosure is sufficient to convey to one of ordinary skill in the art that the inventor had possession of the invention and to enable such a person to practice invention without undue experimentation.

8. Morrison & Foerster LLP has asked me to opine, based on the documents cited in this report, the assumptions stated herein, and my expertise in the field of adenoviruses, as to the sufficiency of the disclosure of the '512 application (Ex. 2002) and the associated priority documents and the clarity of the claims pending in that application, viewed from the perspective of one of ordinary skill in the art at the relevant period. Specifically I have considered:

- The attributes of a person of ordinary skill in the art in 1996-1999;
- The state of knowledge in the field of animal adenoviruses during that time;
- The extent to which the Australian Provisional Patent Application No. PO 8560 (Ex. 2003) filed August 14, 1997, by Johnson et al., (the "AU application") describes an embodiment of Count 1 of the interference, and whether a person of skill in the art in August 1997 would have been able to make an embodiment using the teachings of the AU application as a guide;
- The extent to which the inventions claimed in the '512 application (Ex. 2002) are described in the specification, and whether a person of skill in the art in

- 1998 would have been able to make embodiments within the full scope of the claims using the teachings of the '512 application (Ex. 2002) as a guide; and
- The extent to which the scope of the claims of the '512 application (Ex. 2002) would have been clear to a person of skill in the art in 1998 when reading the claims in light of the specification.

**A. Characteristics of a Person of Ordinary Skill In The Art In 1996-1999**

9. The art relevant to the technology at issue in this interference is the preparation of animal adenovirus-based vectors for administration to mammals. In my opinion, a person having ordinary skill in this art in 1996-1999 would have had at least a Master's degree in the biological sciences and/or a Bachelor's degree with at least two years of experience in adenoviruses and have been familiar with scientific and technical publications concerning animal adenoviruses and in particular, porcine adenoviruses.

**B. Adenoviruses**

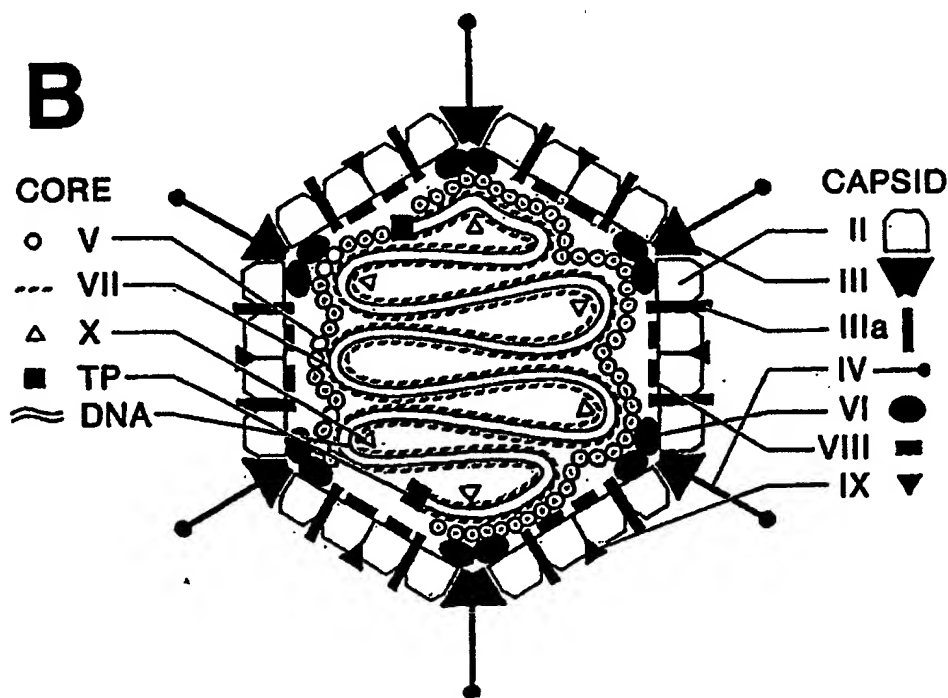
10. Adenoviruses are DNA viruses that infect a large variety of animals and birds. Known adenoviruses include human ("HAV"), porcine ("PAV"), bovine ("BAV"), mouse ("MAV"), and many others. Multiple strains, or "serotypes," of each of these types of adenoviruses are known to exist. These are referred to by number. For instance, human adenovirus serotype 2 is referred to as HAV2. As of August 1997, certain adenoviruses were well characterized in the art. (Ex. 2014 Thomas Shenk, Ch. 67: *Adenoviridae: The Viruses and Their Replication*. FIELDS VIROLOGY, 2111-48 (3<sup>rd</sup> ed., B.N. Fields et al. eds. Lippincott – Raven Publishers, Philadelphia, 1996)).

11. Since 1987, researchers have studied the potential use of adenoviruses as vectors for the delivery and expression of foreign DNA. (Ex. 2015 Jean-Luc Imler et al., *Trans-*

*Complementation of E1-Deleted Adenovirus: A New Vector To Reduce The Possibility Of Codissemination Of Wild-Type And Recombinant Adenoviruses.* HUMAN GENE THERAPY 6, 711-721 (1995); Ex. 2016, Marshall S. Horwitz, Ch. 68: *Adenoviruses*, FIELDS VIROLOGY B. N. Fields B.N. et al. eds. Lippincott – Raven Publishers, Philadelphia, 2149-71, 2165 (1996)).

12. This is true in part because certain adenoviruses are known to be relatively harmless to the infected immunocompetent human or animal, but highly effective in stimulating an immune response. (See, e.g., Ex. 2020, T. Tuboly et al., *Potential Viral Vectors For The Stimulation Of Mucosal Antibody Responses Against Enteric Viral Antigens In Pigs*, RESEARCH IN VETERINARY SCIENCE 54, 345-50 (1993)). Scientists realized that a benign adenovirus might be recombined with DNA encoding antigens of more virulent pathogens in order to create a vaccine.

13. Adenoviruses have icosahedral capsids that are composed of proteins, as is shown in the representation below:



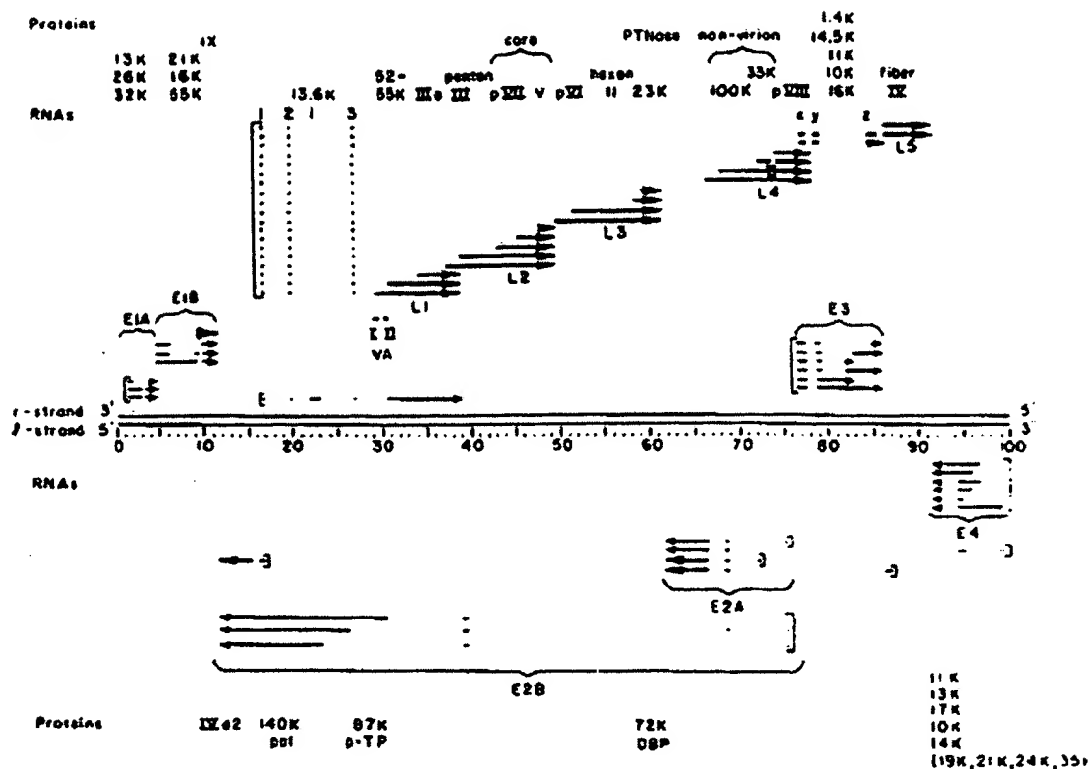
(Ex. 2014, Shenk et al., *supra* at 2115, Figure 2B).

14. Capsid proteins are critical structural elements that the virus requires to survive. By convention, the proteins that comprise the adenovirus are identified by Roman numerals, as shown above. Thus, for example, pVIII refers to capsid protein numeral VIII, shown above. The major capsid proteins are also known by other names such as "fiber" for pIV, "hexon" for pII, and "penton" for pIII. (Ex. 2014, Shenk et al., *supra* at 2116, Figure 3)

15. The adenovirus genome consists of a single linear, double-stranded DNA. (Ex. 2014, Shenk et al., *supra* at 2115, paragraph bridging left and right columns). Transcription of adenovirus DNA is accomplished in two phases: the early phase and the late phase. During the early phase, the virus selectively transcribes certain "early genes" that perform a variety of functions to create the necessary pre-conditions for viral replication. By convention, the early genes are identified by number E1 through E4.

16. Once early phase transcription is complete, transcription of the "late genes" may begin. The products of late genes include the capsid proteins.

17. Viral DNA is transcribed in blocks known as transcription units, which can be processed into multiple mRNAs. A single mRNA contains at least one "open reading frame," which can be translated into a protein. The open reading frame for one protein may overlap with the open reading frame for another. As a result, in a virus the same sequence of nucleotides may be part of more than one open reading frame. The arrangement of "open reading frames" or genes on a viral genome is commonly illustrated in a "genome map." Reproduced below is the genome map of the human adenovirus serotype 2 (HAV2), as it was understood before August 1997.



(Ex. 2014, Shenk et al., *supra* at 2116, Figure 3)

18. The genome map reproduced above employs the convention of “map units.” A map unit corresponds to one percent of the whole genome length, shown in the x-axis of the map above. Thus, the specific point to which a given map unit (for example, 81) refers depends on the size of the genome. Map unit 81 refers to the 810th base in a genome of 1000 bases, and to the 4,050th base in a genome of 5000 bases, for example.

19. As shown above, HAV2 has five early regions (numbered E1A, E1B, E2 (E2A, E2B), E3, and E4) and five late regions (numbered L1 through L5). (Ex. 2014, Shenk et al., *supra* at 2115, right column, first full paragraph). Each mRNA within each region is represented by an arrow. The body of the arrow represents the nucleotides that are transcribed to produce the mRNA. The direction of the arrow represents the direction of transcription. As is clear from the

diagram shown above, a given nucleotide sequence may be transcribed into a primary transcript that is processed in multiple ways to produce several different mRNAs within a given region. Further, regions may overlap. For example, as shown above, in HAV2 the L4 region and the E3 region overlap. As a result, in HAV2 the same sequence of nucleotides will be involved in expressing both the early region genes of E3 and the late region genes of L4. The number and arrangement of early and late regions vary among adenovirus types and serotypes.

20. As shown at the top of the genome map, the late regions of HAV2 encode structural proteins such as pVIII, which are essential for production of viral particles. (Ex. 2014, Shenk et al., *supra* at Figures 2B and 3, and 2113-2116).

21. The early genes, by contrast, generally encode proteins responsible for replication and transcription of the viral genome, and interactions with the host cell and host immune response. (Ex. 2014, Shenk et al., *supra* at Figure 5, at 2119). For instance, in HAV2, the E3 gene encodes proteins that modulate the response of the host cells to the adenovirus infection. (Ex. 2014, Shenk et al., *supra* at 2117, left column, lines 18-20). In some circumstances, the products of early region genes may not be needed for efficient viral growth in cultured cells. (Ex. 2014, Shenk et al., *supra* at 2134, sentence bridging left and right columns)

22. As discussed above, for nearly 20 years scientists have been experimenting with recombinant techniques to insert foreign DNA into adenoviruses. Depending on where in the genome the foreign genes are inserted, they may disrupt the expression of one or more of the adenovirus's genes. In some cases, the genes that are disrupted may be essential to the formation of the adenovirus. In such cases, the recombinant adenovirus cannot form except in the presence of a "helper" cell or a "helper virus" that is designed to supply the missing protein or proteins

that are associated with the disabled gene or genes. (see Ex. 2016, Horwitz, *supra* at 2165-2166).

23. For example, human adenoviral vectors with insertions in the essential region E1 are produced in complementing cell lines such as the human embryonic kidney "293" cell line, which expresses E1 proteins. (Ex. 2017, F. L. Graham, F. L., et al., *Characteristics Of A Human Cell Line Transformed By DNA From Human Adenovirus Type 5*, JOURNAL OF GENERAL VIROLOGY 36, 59-72 (1977); (see Ex. 2016, Horwitz, *supra* at 2166, right column, last ¶).

24. However, by experimentation it is also sometimes possible to identify certain areas of the adenovirus genome that are not essential to viral replication. When insertions of foreign DNA are made in these regions, the result may be a "helper-independent" recombinant adenovirus. For example, in HAV2, the E3 region of human adenovirus was found to be non-essential for growth in tissue culture. Accordingly, it is possible to create a helper-independent virus by making insertions of foreign DNA in the E3 region of HAV2. (see Ex. 2016, Horwitz *supra* at 2165, right column)

25. As discussed above, however, a given nucleotide sequence may be involved in the expression of multiple genes, some of which may be essential to viral replication, and some of which may be non-essential. Moreover, types and serotypes of adenoviruses vary significantly from one another in terms of the number of genes, their location in the genome, and the extent to which the proteins that they encode are necessary for viral replication. It is necessary to have precise knowledge of the genome of the particular type and serotype of adenovirus under investigation in order to predict which genes may be disrupted by insertions of foreign genes in a given location, or to predict which insertions are likely to render the virus replication-defective.

26. Adenoviruses have a limit to the amount of DNA that they can encapsidate. (Ex. 2035, Andrew J. Bett et al., *Packaging Capacity and Stability of Human Adenovirus Type 5 Vectors* JOURNAL OF VIROLOGY 67(10) 5911-5921 (1993)). In order to make room for foreign genes, it is sometimes useful to delete portions of the native adenovirus DNA. As in the case of insertions of foreign DNA, this may prevent the expression of any genes that are associated with the deleted nucleotides. If so, then the resulting adenovirus will not assemble into an infectious recombinant adenovirus particle except in a suitable complementary helper cell line.

### C. Porcine Adenovirus 3

27. The patents at issue in this interference proceeding relate to porcine adenoviruses ("PAV"). At least five different serotypes of PAV were known to exist in 1995, although none had been fully characterized. (see Ex. 2018, J. B. Derbyshire, et al. *Serological And Pathogenicity Studies With Some Unclassified Porcine Adenoviruses*, JOURNAL OF COMPARATIVE PATHOLOGY 85, 437-443 (1975); and see Ex. 2019, Tadashi Hirahara et al., *Isolation Of Porcine Adenovirus From The Respiratory Tract Of Pigs In Japan*, JAPANESE JOURNAL OF VETERINARY SCIENCES 52: 407-409 (1990)).

28. Porcine adenoviruses have minimal pathogenicity. At least by 1993 they had been proposed as vectors for viral vaccines. (Ex. 2020, Tuboly et al., *supra* at 345-350). In particular, the serotype PAV3 was thought to be a suitable vector based on its low virulence and the ability to grow well in cell culture. (See, Ex. 2020, Tuboly et al.).

29. Compared to its human adenovirus counterparts, relatively little was known about PAV3 as of August 1997. By that time, Reddy had isolated the PAV3 genome, determined its restriction map and cloned fragments representing the entire genome. (Ex. 2021, P. Seshidhar Reddy, et al., *Restriction Endonuclease Analysis and Molecular Cloning of Porcine Adenovirus*

Type 3. INTERVIROLOGY 36, 161-168 (1993), *see also Id.* at 162, 1<sup>st</sup> ¶, last sentence). Reddy had also prepared a map showing generally where enzyme cleavage sites occur within the genome, *Id.* at page 166, Figure 4.

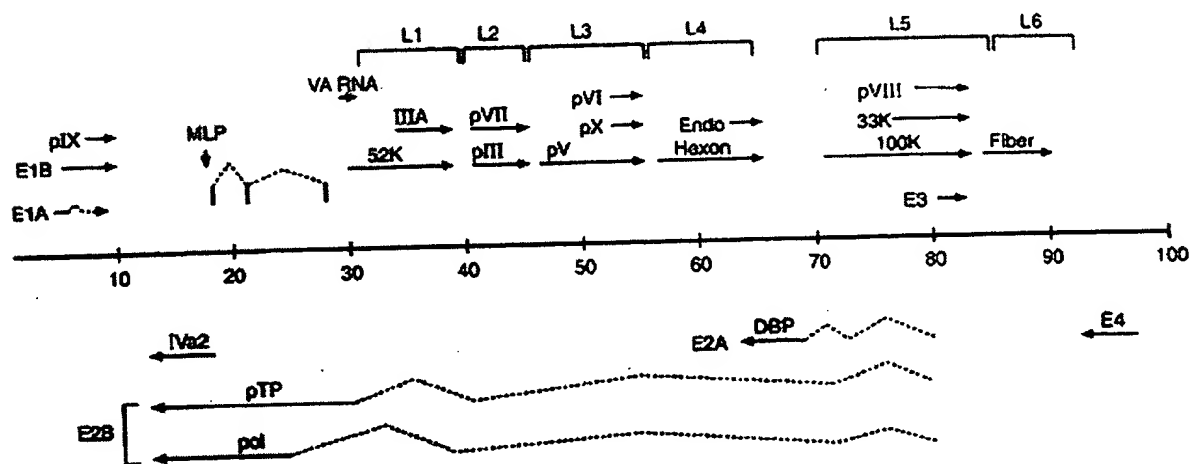
30. In addition, certain segments of the genome had been sequenced. Specifically, as of August 1997:

- The region encoding pVIII, E3 and fibre regions of PAV3 were sequenced by 1995 by Reddy and others. (Ex. 2022, P. Seshidhar Reddy et al., *Sequence Analysis of Putative pVIII, E3 and Fibre Regions of Porcine Adenovirus Type 3*, VIRUS RESEARCH 36, 97-106, *see also* abstract (1995)).
- The inverted terminal repeat (ITR) sequences flanking PAV genomes were also sequenced by 1995 by Reddy and others. (Ex. 2023, P. Seshidhar Reddy et al., *Comparison of Inverted Terminal Repetition Sequences From Five Porcine Adenovirus Serotypes*, VIROLOGY 212, 237-239 (1995) and Figure 1, at page 238).
- A comparison of the E3 regions of PAVs-1, 2 and 3 had been published in 1996 by Reddy and others. (Ex. 2024, P. Seshidhar Reddy et al., *Porcine Adenovirus Types 1, 2 And 3 Have Short And Simple Early E-3 Regions*, VIRUS RESEARCH 43, 99-109 (1996)).
- The E4 region of PAV3 had been sequenced and 5' and 3' ends of transcripts characterized by 1997 by Reddy and others. (Ex. 2025, P. Seshidhar Reddy et al., *Characterization of the early region 4 of porcine adenovirus type 3*, VIRUS GENES 15, 87-90 (1997)).
- The sequences of the late PAV3 gene encoding the structural protein penton and the 23K endopeptidase were published in 1996. ((Ex. 2026, R. J. McCoy, et al.,

*Genomic Location And Nucleotide Sequence of A Porcine Adenovirus Penton Base Gene*, ARCHIVES OF VIROLOGY 141, 1367-1375 (1996), and Ex. 2027, R. J. McCoy et al., *Nucleotide And Amino Acid Sequence Analysis Of The Porcine Adenovirus 23K Protein*, DNA SEQUENCE 6, 251-254 (1996)).

- The sequence of the late PAV3 gene encoding the 100K protein was published in 1997. (Ex. 2028, R. J. McCoy et al. *Nucleotide and Amino Acid Sequence Analysis of the 100K Protein of a Serotype 3 Porcine Adenovirus*, DNA SEQUENCE 8, 59-61 (1997)).

31. Below is the genome map of PAV3 that Reddy published in 1998 (Ex. 2029, P. Seshidhar Reddy et al., *Nucleotide Sequence And Transcription Map Of Porcine Adenovirus Type 3*, VIROLOGY 251(2):414-426, 420, at Figure 1 (1998)).



32. As of August 1997, the full sequence of PAV3 was not known, and there was no published genome map of the kind shown above available to show how the various regions and genes of the genome are arranged. Nor was the exact size of the genome known.

33. In the absence of this information, researchers in the field sometimes relied on their understanding of well-known adenovirus types and serotypes for clues about the structure of PAV3. For instance, the overall genome organization of PAV3 is similar, but not identical, to HAV2. (See, Ex. 2022, Reddy et al.)

34. However, such a comparison is not reliable for making specific predictions about the structure of PAV3 because homology among types of adenovirus, or even among serotypes (e.g. PAV3 and PAV4) is not strong. (Ex. 2022, Reddy et al., *supra* at 104-105; see Ex. 2024, Reddy et al.) For instance, distinctive features of the PAV3 genome not found in HAV2 include the organization of late region genes into six families instead of five, the absence of additional leader sequences in transcripts of the fibre gene, and the presence of a single small virus-associated RNA gene. (Ex. 2029, right column, at lines 8-15 (1998)).

35. The nucleotide sequence and transcription map of the entire PAV3 genome was first published in 1998 by Reddy and others and revealed that the PAV3 genome is 34,094 base pairs long. (Ex. 2029, Reddy et al., *supra* in the abstract.) The '343 patent (Ex. 2001) includes a disclosure of the sequence and transcription map of the entire PAV3 genome. (Figure 1 (sequence) and Figure 2 (transcription map) of the '343 patent.)

**D. The Claims of the '512 Application (Ex. 2002) Are Not Clearly Defined**

36. All of the claims of the '512 Application specify that insertions of foreign DNA must be made within certain map unit ranges. For instance, Claim 1 of the '512 application (Ex. 2002) is directed to recombinant PAV3 where the insertion site is "selected from the group consisting of one or more mapping units selected from the group consisting of mapping units 50-55, 55-65, 72-85, 81-84, and 97-99.5 of PAV3." All of the claims in interference specify that an insertion is to be made into at least one of these map-unit ranges (Ex. 2013).

37. As discussed above, map units are defined relative to the overall size of the genome. Accordingly, the precise nucleotides corresponding to map units specified in the claims of the '512 application (Ex. 2002) can only be determined on the basis of the genome size. However the '512 application discloses three different sizes of the PAV3 genome. These are 34.8 kb (page 3, line 28), 35kb (Fig. 1) and 34.094 kb (Fig. 15) (Ex. 2002). The '512 application does not indicate which of these three sizes of PAV3 is intended to be the basis of the map units specified in the claims. Accordingly, the use of map units in the claims of the '512 application (Ex. 2002) does not teach a defined nucleotide region of the genome to a person of ordinary skill in the art.

38. It is now known that the correct size of the PAV3 genome is in fact 34,094 bp. (Ex. 2029, Reddy et al., *supra* entire article, but especially at 414-415).

39. Claim 30 of the '512 application (Ex. 2002), which is directed to insertions made in the range of map units 81-84, is illustrative of why Johnson's failure to identify a consistent genome size for PAV3 renders the claims unclear. Using the 34.8 kb genome size that Johnson attributed to PAV3 prior to Reddy's publication of the complete PAV3 genome, map units 81-84 would be defined by a scale of 348 nucleotides per map unit. Thus, map unit 81 would correspond to nucleotide 28,188, and map unit 84 would correspond to nucleotide 29,232. Accordingly, one might conclude that the scope of Claim 30 encompasses PAV3 in which foreign genes are inserted between nucleotides 28,188 and 29,232.

40. However, based on the correct size of 34,094 bp, disclosed in Fig. 15 of the '512 application (Ex. 2002), each map unit would be 340.94 nucleotides. According to this scale, nucleotide 28,188 would correspond to map unit 82.6 and nucleotide 29,232 would correspond to map unit 85.73. Thus the nucleotides specified by map units "81-84" when the PAV3 genome is

considered to be 34.8 kb are actually the nucleotides corresponding to map units 82.6 to 85.73 when the correct PAV3 size is used. The shift in the domain of the map unit range is sufficient to partly encompass nucleotides associated with the essential fiber gene. According to Reddy 1998, the fiber gene of L6 begins at nucleotide 28,910 (Ex. 2029, Reddy, *supra* "splice acceptor site" at page 415, Table 2).

41. Each of the map unit ranges specified in the claims of the '512 Johnson application (Ex. 2002) would be similarly affected by the selection of the genome size as shown in Table 1 below. Based on yet another genome size of 35 kb disclosed in Fig. 1 of the Johnson '512 application, map unit ranges correspond to another set of nucleotides shown in Table 2 below. Thus, 81-84 map units represent nucleotides 28,188 – 29,232 based on a 34,800 bp PAV-3 genome size disclosed on page 3, line 28 of the '512 application, nucleotides 28,350 – 29,400 based on a 35,000 bp PAV-3 genome size disclosed in Fig. 1 of the '512 application, and nucleotides 27,616 – 28,639 based on a 34,094 bp PAV-3 genome size disclosed in Fig. 15 of the '512 application (Ex. 2002, page 3, line 28, and Figs. 1 and 15).

Table 1			
MAP UNITS	Corresponding nucleotides based on PAV-3 genome size of 34.8 kbp	"Map units" corresponding to the nucleotides in column 2, based on correct size of PAV-3 genome (34,094 bp)	Nucleotides corresponding to Map Units in column 1, based on correct size of PAV-3 genome (34,094 bp)
50 – 55	17,400 – 19,140	51.04 – 56.14	17,047 – 18,752
55 – 65	19,140 – 22,620	56.14 – 66.35	18,752 – 22,161
72 – 85	25,056 – 29,580	73.49 – 86.76	24,548 – 28,980
81 – 84	28,188 – 29,232	82.68 – 85.74	27,616 – 28,639
97 – 99.5	33,756 – 34,626	99.01 – 101.56	33,071 – 33,924

<b>Table 2</b>		
<b>MAP UNITS</b>	<b>Corresponding nucleotides based on PAV-3 genome size of 35 kbp</b>	<b>"Map units" corresponding to the nucleotides in column 2, based on correct size of PAV-3 genome (34,094 bp)</b>
<b>50 – 55</b>	17,500 – 19,250	<b>51.33 – 56.46</b>
<b>55 – 65</b>	19,250 – 22,750	<b>56.46 – 66.73</b>
<b>72 – 85</b>	25,200 – 29,750	<b>73.91 – 87.26</b>
<b>81 – 84</b>	28,350 – 29,400	<b>83.15 – 86.23</b>
<b>97 – 99.5</b>	33,950 – 34,825	<b>99.58 – 102.14</b>

42. Thus, there is a range of results that a person of skill in the art might obtain when interpreting the scope of the claims in light of the different genome lengths recited in the specification. It is not clear which genome insertions fall within the scope of the claims, and which do not.

**E. No Embodiment of the Invention of Count 1 is Described or Enabled by the Disclosures of the AU Application (Ex. 2003)**

**1. The AU Application (Ex. 2003) Discloses Only Helper-Independent Recombinant PAV3**

43. Johnson's AU patent application (Ex. 2003) discloses a recombinant PAV3 with foreign genes inserted into non-essential regions of the genome for the purpose of creating helper-independent viral vectors.

44. The AU patent application (Ex. 2003) discusses insertion only into non-essential regions. ("The DNA of interest which may comprise heterologous genes coding for antigenic determinants or immuno-potentiator molecules may be located in at least one non-essential region of the viral genome." p. 6, lines 13-15 of AU application). It does not discuss insertion of foreign sequences into essential regions of the genome, and does not disclose helper cell lines capable of replicating helper-dependent viruses.

45. A person of ordinary skill in the field of adenoviruses in 1997 could not have created helper-dependent viruses and complementing cell lines based on the teachings of the AU application (Ex. 2003) without extensive experimentation.

**2. The AU Application (Ex. 2003) Does Not Describe Inserting Foreign Genes Into The E3 Region.**

46. Count 1 of the interference is directed to a recombinant PAV3 incorporating foreign DNA in the E3 region.

47. The AU application (Ex. 2003) states that the E3 region is non-essential and suggests that it might be suitable for insertion "after the polyadenylation signal" of the "overlapping L4" region: "The E3 region of the genome, this also being a non-essential area, has been located and cloned. The promoter region of E3 has been identified and the overlapping L4 area sequenced (Figure 5). The region of the E3 after the polyadenylation signal of the L4 is also a possible site for insertion and can also be used for deletion to create more room for larger cassette insertions." (p. 14 lines 4-9.) Similarly, at page 11 lines 2-3, the Figure 5 sequence purports to show "the promoter region of E3 and the overlapping L4 area." These statements do not disclose an embodiment within the scope of the Count, for several reasons.

48. First, in PAV3, the E3 region does not overlap with L4. The AU application (Ex. 2003) cites a Kleiboeker 1994 paper (Ex. 2030) demonstrating that the layout of PAV4 was similar to human adenoviruses in the area of the L4 and E3 regions (p. 4 lines 25-29.); Fig. 2 (Ex. 2030, Steven B. Kleiboeker, *Sequence Analysis of Putative E3, pVIII, and Fiber Genomic Regions of a Porcine Adenovirus*, VIRUS RESEARCH, 31:17-25 (1994)). As shown in the diagram in paragraph 17 above, in HAV2, L4 overlaps E3. Thus, Johnson may have assumed that E3 would overlap L4 based on his understanding of HAV2. But in PAV3, E3 overlaps with the L5 region, not the L4 region. (see Ex. 2029 at Figure 1, reproduced supra at paragraph 31, Fig. 2 of

the '343 patent (Ex. 2001) and Exhibit A, the declaration of J. Hammond, Feb. 26, 2004, submitted by Johnson in the prosecution of the '512 application (Ex. 2033)).

49. Second, even if the reader were sufficiently skilled to recognize that L4 in this context should be understood to be L5, it would be impossible to follow the teaching of the patent to make an insertion in the region of the E3 after the polyadenylation signal of L5. The end of a messenger RNA is formed 10 to 30 nucleotides downstream of the polyadenylation signal which is a specific nucleotide sequence (AAUAAA). Thus, the polyadenylation signal is found 10-30 nucleotides upstream from the end point of the genes associated with a given region. As a result, genes that share a common polyadenylation signal are co-terminal. In PAV3 (unlike HAV2), the E3 region and the L5 region are co-terminal – they share the *same* polyadenylation site, which is present at the very end of the E3 region. (Ex. 2022, Reddy et al., *supra* at Figures 1 and 2, and page 100; Ex. 2024, Reddy et al. (1996) at 106 and Figure 7; Ex. 2029, Reddy et al. (1998) at Table 2; and Ex. 2036, P. Seshidhar Reddy et al., *Development of Porcine Adenovirus-3 as an Expression Vector*, JOURNAL OF GENERAL VIROLOGY 80, 563-570, at 569 (1999)). (In PAV4, by contrast, there is an additional polyadenylation site toward the beginning of the E3 region that signals the termination of L4 transcription.) Thus, in PAV3 *none* of the E3 region is after the polyadenylation site for L5. The AU application's instructions to use "the region of the E3 after the polyadenylation signal" therefore does not specify any portion of E3 for use as an insertion site (Ex. 2003, *supra* at page 14, lines 6-7).

50. In sum, the AU application directs the reader to make an insertion in E3 after the polyadenylation signal of overlapping L4 region (Ex. 2003, *supra* at page 14, lines 5-6, and Figure 5), but in PAV3: (1) it is the L5 region, not the L4 region, that overlaps E3, and (2) E3

terminates at the polyadenylation signal of L5, leaving no part of the E3 region that is "after the polyadenylation signal" of L5 (Ex. 2029, Reddy, *supra* at page 416, Figure 1).

51. Nothing else in the AU application describes the insertion of foreign DNA into the E3 region of PAV3 (Ex. 2003). No example of a recombinant virus constructed by insertion of foreign DNA into the E3 region is given that would demonstrate the non-essential region of E3. Figure 5 of the AU application illustrates the organization and restriction map of a 1618 bp fragment labeled "PAV3 E3 sequence." (Ex. 2003, AU application, *supra* at Fig. 5, page 11 lines 2-3). However, Figure 5 clearly is not limited to E3, because E3 is significantly smaller than 1618 bp. (Ex. 2022, Reddy et al., *supra*). It also does not identify where E3 begins and ends in relation to the three overlapping segments, and it does not show any gene sequences.

52. Based on the above, I conclude that the AU application does not indicate that Johnson possessed a recombinant PAV3 vector incorporating foreign DNA into the E3 region of the genome, much less in the specific 81-84 map unit portion of E3 (Ex. 2003). Johnson's only suggestion to make such an insertion – after the overlapping polyadenylation signal of L4 – is impossible to carry out.

**F. The Full Scope of the Claims of the '512 Application (Ex. 2002) Are Not Described or Enabled.**

53. I have been asked to consider whether the '512 application (Ex. 2002) adequately discloses and enables a person of ordinary skill in the art to practice the full scope of Johnson's claims in interference. I conclude that it does not.

54. Claim 1 of the '512 application (Ex. 2002) is directed to a PAV3 vector where the insertion site is "selected from the group consisting of one or more mapping units selected from the group consisting of mapping units 50-55, 55-65, 72-85, 81-84, and 97-99.5 of PAV3." All of Johnson's claims contain one or more map unit limitations of the kind included in Claim 1.

Below, I consider the claims in four groups: (1) claims 1-4, 26, 31, 39-40, 42, 44-65, 67, 68-69, and 72-73 directed to insertions in the group of map units 50-55, 55-65, or 72-85, (2) claims 28 and 71 directed to insertions into map units 81-84, (3) claim 30 directed to insertions into map units 97-99.5, and (4) claim 26, directed to the insertion into “non-essential regions” of PAV3.

**1. The '512 Application (Ex. 2002) Does Not Describe or Enable PAV3 Incorporating Foreign DNA at Insertion Sites MU 50-55, 55-65, or 72-85.**

55. Claims 1-4, 26, 31, 39-40, 42, 44-65, 67, 68-69, and 72-73 each specify that insertion of the foreign DNA is to be made in one or more of the map unit ranges 50-55, 55-65, or 72-85 (Ex. 2002, *supra* at page 22-26, and preliminary amendment at pages 1 and 2).

56. Map units 50-55, 55-65, and 72-85 are not mentioned or otherwise described anywhere in the '512 application, and it does not incorporate by reference publications that disclosed the sequences of these regions. The '512 application teaches insertion of “cassettes” of heterologous DNA that include polyA signals which signal the end of transcription. (Ex. 2002).

57. Map units 50-55, 55-65, 72-85 correspond to areas of PAV3 that are predicted to be essential for viral replication based on what was known about human adenovirus type 2. (Ex. 2014, Shenk, *supra* at 2131, right column) Specifically, they encompass coding regions for PAV3 proteins: pVI, pX, pV, endopeptidase, hexon, pVIII, 33K and 100K. (Ex. 2029 at Figure 1). None of these genes are known to be non-essential for PAV3 replication, and the '512 application (Ex. 2002) does not teach the locations and characterizations, if any, of non-essential regions within map units 50-55, 55-65, 72-85 of PAV3.

58. Accordingly, insertions made in these map unit regions are highly likely to disrupt the expression of one or more of these genes, thus rendering the product replication-defective.

59. Nothing in the '512 application teaches the use of helper cell lines which would make it possible for a person of ordinary skill in the art to grow a replication-defective PAV3 (Ex. 2002). In August 1997, no helper cell lines for growing any replication-defective form of PAV3 were available. Extensive experimentation is required to produce a new helper cell line. (Ex. 2016, Horwitz, *supra* at 2166).

60. Thus, in my opinion the teachings of the '512 application (Ex. 2002) do not enable one of skill in the art how to make and use a PAV3 vector with insertions within map units 50-55, 55-65, 72-85 without undue experimentation. They also do not clearly convey that Johnson had possession of any recombinant PAV3 incorporating foreign DNA into any of these map unit ranges.

**2. The '512 Application (Ex. 2002) Does Not Enable PAV3  
Incorporating Foreign DNA at Map Units 97-99.5**

61. Johnson claims 28 and 71 of the '512 application are directed to a recombinant PAV3 incorporating heterologous DNA in the region identified as encompassing map units 97 to 99.5 Representative claim 28 reads:

A recombinant vector as claimed in claim 2 wherein said heterologous DNA is stably integrated into the right hand end of the genome at map units from about 97 to about 99.5.

The '512 application (Ex. 2002, *supra* at page 5, lines 18-19) teaches that map units 97-99.5 encompass:

[n]on-essential regions of the viral genome which may be suitable for the purposes of replacement with or insertion of heterologous nucleotide sequences[.]

62. The '512 application discloses a non-essential region where insertions can be made as "regions at the right terminal end of the genome at map units 97-99.5." (Ex. 2002, *supra*, at p. 5, line 18-20). It purports to further specify the area for insertion in Figure 4, which

allegedly identifies the putative TATA site for the E4 promoter, "this being the left most end for the possible site of insertion." (*Id.* at p. 11, lines 29-30). A TATA site is a sequence of nucleotides (literally "TATA") that is essential for the expression of the genes that are associated with it.

63. E4 plays major roles in late gene expression and regulation of transcription. (Ex. 2025, Reddy et al., *supra* at 87). Since E4 is an essential region, an insertion downstream of the TATA site could disrupt E4 expression and destroy the PAV3 vector's ability to replicate.

64. Figure 4 of the AU application identifies the referenced TATA site in bold type at nucleotides 698-701 (Ex. 2003). The map unit range of 97 to 99.5 approximates the area between the bolded ITR (nucleotides 1-144) and the bolded TATA site in Figure 4.

65. The TATA site called out in Figure 4 of the AU application (Ex. 2003), however, is not the TATA site for E4 transcription. Ex. 2025 (Reddy, *supra* at page 88, Figure 1) showed a physical map of the PAV3 genome of a 3028 nucleotide fragment encompassing the right end of the genome. In this figure, Reddy identified features including the locations of the right hand ITR, the E4 region, the polyA signal and two TATA sites corresponding to putative transcription initiation sites. (*Id.*)

66. Pages 88-89 of the Reddy article report the results of experiments to determine the 5'-end of the E4 transcripts (Ex. 2025). The data indicate that transcription initiates 22-24 nucleotides downstream from the 3' end of the TATA box between nucleotides 324 and 327. (Ex. 2025, Reddy et al., *supra* at 88-89.) Thus, the active TATA site for E4 corresponds to nucleotides 324-327 shown in Figure 4 of Johnson's AU application (Ex. 2003).

67. Thus, claims 28 and 71 of the '512 Johnson application (Ex. 2002) encompass within their scope portions of E4 that are essential to viral replication – namely portions of the

E4 region genes, including the TATA site of E4. Accordingly, some of the embodiments of these claims could disable the E4 region genes, rendering the virus helper-dependent. To practice the full scope of these claims, it would be necessary to provide a helper cell line capable of replacing the function of the disabled E4 genes.

68. Because, as discussed above, the '512 application (Ex. 2002) does not describe a suitable helper cell line or enable a person of skill in the art to produce such a cell line without undue experimentation, in my opinion the teachings of the '512 Application do not enable one of skill in the art how to make and use a PAV3 vector with insertions within the full range of map units 97-99.5 without undue experimentation.

**3. The '512 Application (Ex. 2002) Does Not Enable PAV3 Incorporating Foreign DNA in a Non-coding Region of E3 After the Polyadenylation Signal of L5, and Does Not Enable Replication of Replication-Defective Recombinants.**

69. As discussed above, the '512 Application describes the range of 81-84 as being a "non-coding region" (Ex. 2002, at page 5, lines 20-21) that overlaps with L4 (*id.* at page 11, line 33). On the contrary, all of the region between 81 and 84 map units (defined relative to the correct genome size of PAV3) is predicted to be a protein coding region. Further, E3 does not overlap with L4.

70. The '512 Application also suggests inserting foreign DNA into the E3 region after the polyadenylation signal of L4. (Ex. 2002, at page 11, bridging sentence to page 12) Even if a person of skill in the art interpreted the term "L4" in the '512 Application to refer to L5 of PAV3, as explained above, it is impossible to insert DNA in to the E3 region after the polyadenylation signal of L5, because in PAV3, L5 shares the polyadenylation signal with E3.

71. The '512 application (Ex. 2002) clearly does not enable a person of skill in the art to insert foreign DNA into a "non-coding region" of E3 after the polyadenylation signal of L5.

72. Further, using the PAV3 genome size disclosed in the AU Application, map unit ranges 81 to 84 correspond to nucleotides 28,188 and 29,232 of PAV3. Encompassed within this range is the gene that encodes for fibre, which is an essential structural element of PAV3. The fibre gene begins at nucleotide 28910. (Ex. 2029 at page 415, Table 2). Accordingly, some embodiments within the scope of this claim are predicted to be replication-defective.

73. The '512 application does not describe or enable the production of replication-defective recombinants of PAV3 (Ex. 2002). A person of ordinary skill in the art would not have been able to propagate replication-defective PAV-3 recombinants without the appropriate helper cells which require undue experimentation to obtain.

**4. The '512 Application (Ex. 2002) Does Not Describe or Enable Insertions Into Non-Essential Regions of PAV3.**

74. Claim 26 of the '512 Johnson application (Ex. 2002) is directed to a recombinant adenovirus wherein the foreign DNA is "integrated into the non-essential regions of the porcine adenovirus genome." The '512 application does not show which regions of PAV3 are non-essential and which are essential. In August 1997, it was not known which regions of PAV3 would prove to be essential for viral replication. Indeed, this is a question that is still under active investigation in the art. Nor is it possible to predict with confidence which regions of PAV3 are non-essential based on an understanding of other PAV serotypes or of non-porcine adenoviruses, because homology between PAV3 and other PAV serotypes is not sufficient to identify essential PAV3 regions based information that may be available regarding other PAV serotypes. Without this information, it is impossible for a person of ordinary skill in the art to practice the full scope of this claim.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Board of Patent Appeals and Interferences of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross examination in the case and that cross examination will take place within the United States. If cross examination is required of me, I will appear for cross examination within the United States during the time allotted for cross examination.

Executed this 24th day of February, 2006.

  
Katherine R. Spindler, Ph.D